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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/553,552	04/20/2000	Robert S. Langer	0492611-0326(8151)	4483

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/11/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/553,552	LANGER ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-32,35,39,41,42,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-32,35,39,41,42,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 24, 2003 has been entered as Paper No. 17.

Claims 1-8, 10-12, 14-18, 20, 29, 30, 32 39, 41, 42, 44 have been amended, claim 46 has been added by the amendment filed November 27, 2002.

Claims 1-12, 14-32, 35, 39, 41, 42, 45, 46 are pending for examination.

Upon a further search of prior art and consideration/examination of the newly amended and added claims, when read in light of the as-filed specification and the state of the prior art as a whole, all previous office actions do not accurately address the inventions as now claimed, and as such, the previous office actions have been substituted by the following office action in which the new grounds of rejection are indicated as follows.

Claims 1, 5, 42 are objected because the recitation of "cis-actonyls" appears to be a typographical error. See originally filed claim 13. A search of prior art does not provide any teaching of the "cis-actonyls". Corrections are requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 14-32, 35, 39, 41, 42, 45, readable on a genus of endosomolytic agents, when read in light of the as-filed specification (page 6), clearly exclude known endosomolytic agents (i.e., chloroquine, fusogenic peptides, inactivated adenoviruses and polyethyleneimine), wherein the agents must exhibit an endosomolytic activity in response to a change in pH, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

All presently pending claims new embrace any polymer comprising an endosmolytic polymer not known in the prior art at the time the invention was made (i.e., chloroquine, fusogenic peptides, inactivated adenoviruses and polyethyleneimine), and one or more hydrolysable functional moieties selected from the group consisting of ortho-esters, hydrazone, and cis-acetonyl, wherein said polymer due to the presence the endosomolytic agent is capable of effecting the lysis of an endosome in response to a change in pH.

The as-filed specification only provides sufficient written description of an endosomolytic polymer comprising monomers having ionizable functional moieties, which comprise proton acceptor sites, operably linked to one or more hydrolysable functional moieties selected from the group consisting of ortho-esters, hydrazones, and cis-acetonyl, wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH. More specifically, the as-filed specification provides two examples of such ionizable functional moieties, *e.g.,* N-methacryloyl-L-histidine and

ethanol. However, the claims are broadly drawn to any polymer comprising any endosomolytic agent, which are yet to be discovered, and one or more hydrolysable functional moieties (ortho-esters, hydrazones, and cis-acetonyl), wherein the hydrolysable functional moieties are not even required to be monomers or part of the endosomolytic agent. The compounds composed of just ortho-esters, hydrzones, and cis-acetonyls do not *per se* exhibit the endosomolytic activity which is the essential feature of the invention. Thus, it is apparent that the main thrust of the presently pending claimed invention, which meets the written description requirement, is a combination of monomers composed of ortho-esters, hydrzones, and cis-acetonyls functionally linked to monomers having ionizable functional moieties, which contain proton acceptor sites. A close review of the as-filed specification only leads a skilled artisan to the invention of an endosomolytic polymer comprising a combination of monomers composed of ortho-esters, hydrzones, and cis-acetonyls functionally linked to monomers having ionizable functional moieties, which contain proton acceptor sites. The description of a endosomolytic polymer comprising a combination of monomers composed of ortho-esters, hydrzones, and cis-acetonyls functionally linked to monomers having ionizable functional moieties is not the same as claiming a genus of endomolytic agents which are generically claimed as to be contained in a polymer, which must exhibit the property of being able to complex with a substance to be delivered into a cell, to transfect a cell through the endosome at a size of less than 150 nm, and to exhibit an endosomolytic activity subsequently thereby releasing the

substance into the cytoplasm in an intact form and sufficient amount of the substance for any beneficial utility.

With respect to claims readable on a genus of packaging agents (claim 17) that must exhibit the biological activity of complexing directly or indirectly with the compounds of 1/ and of packaging and delivering a desire molecule to the cytoplasm of a target cell, the as-filed specification only provides sufficient description of packaging agents composed of cationic polymers either copolymerized with the sufficiently described endosomolytic polymer or forming a mixture with the endosomolytic polymer.

In view of the reasons set forth in the preceding paragraphs, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays (page 11 of the specification) and/or any other unspecified structure containing unspecified compounds and/or packaging agents that are only described by functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to agents(s) with no chemical structure as claimed in the presently pending claims because disclosure of no more than that, as in the instant case, is simply a wish to know the

identity of any and/or all other material(s) of agents other than those known in the prior art, as admitted by the as-filed specification, having the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of material(s) as endosomolytic agents and/or packaging agents, which must possess the biological properties (importing a desire molecule through the endosome to the cytoplasm of a target cell as a result of endosomolysis) as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure structure(s) of material(s) other than , as contemplated and asserted by the as-filed specification to the extent that those polymeric nanoparticles once formed would exhibit the contemplated biological functions (importing and endosomolytic activities), and therefore, conception is not

achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-12, 14-32, 35, 39, 41, 42, 45, 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

1) An endosomolytic polymer comprising monomers having ionizable functional moieties operably linked to one or more hydrolysable functional moieties comprising an ortho-ester, hydrzone, and cis-acetonyl functional group, and wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH;
2) A composition comprising a polymeric carrier and the polymer of 1/;
3) A cell delivery composition comprising the polymer of 1/ and a compound to be delivered to a cell;
4) A method of employing the endosomolytic polymer of 1/ to lyse an endosome; and
5) A method of delivery a compound to a cell comprising administering the composition of 3/ to a cell.
6) A method for introducing a nucleic acid into a cell, the method comprising delivery to a cell a biocompatible delivery composition comprising a polymeric carrier, which comprises a nucleic acid and the endosomolytic polymer of 1),

wherein the nucleic acid is delivered into the endosome of the cell and subsequently released from the endosome into the cytoplasm of said cell.

7) A polymeric nanoparticle comprising ethanol as an endosomolytic compound and one or more hydrolysable functional moieties comprising an ortho-ester, hydrzone, and cis-acetonyl functional group, wherein the one or more hydrolysable functional moieties are operably linked to the polymeric nanoparticle, and wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH.

The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all structure other than those as indicated in the enabling embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of endosomolytic agents and/or packaging agents), particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention so that it would operate as intended, *e.g.* functions as a delivery vector to deliver any compound to the cell cytoplasm intact through an endosome of cell targeted for delivery. Additionally, while claim 46 specifically claims that the endosomolytic agent is ethanol, the claims embraces embodiments wherein the hydrolysable functional groups are not necessarily

to be operably linked to the polymer that contains ethanol as an endosomolytic compound. On page 8, the as-filed specification appears to only provide sufficient guidance for a skilled artisan to construct polymeric nanoparticles comprising a polymer operably linked to any of the claimed hydrolysable functional group so as to encapsulate ethanol, and only when the nanoparticles are in the endosome, the employed hydrolysable functional group hydrolyses, releases the endosomolytic compound ethanol, and this is transformed into a hydrophilic diol functionality which is capable of effecting escape from the endosomal compartment into the cytoplasm. Further, claim 42 embraces targeted delivery of a nucleic acid into any subcellular component other than the endosome, however, the entire as-filed specification only provides sufficient guidance for teaching the delivery of a nucleic acid choice into the cytoplasm from the endosome after endocytosis.

As such, it is not apparent how a skilled artisan practices the full breadth of the claimed invention without any undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 14-32, 35, 39, 41, 42, and 45 are rejected under 35 USC 103(a) as being unpatentable over PACK *et al.* (US 2001/0006817) taken with Thorpe (US Pat No. 5,762,918).

The main thrust of the invention is a cell delivery composition comprising a polymeric carrier comprising any biologically active agent such as a nucleic acid and an endosomal lysing polymer, wherein the endosomal lysing polymer comprises ionizable functional moieties operably linked to one or more hydrolysable functional moieties comprising an ortho-ester, hydrzone, and cis-acetonyl functional group.

PACK *et al.* teaches a cell delivery composition comprising a polymeric carrier, which comprises an endosomolytic polymer having ionizable functional moieties or monomers, and a biological active agent such as drugs and nucleic acids, wherein the polymer can be funtionalized so as to link to any desire polymer or factor, and wherein the polymeric carrier can be biocompatible and/or biodegradable mixed, linear, branched, or dendritic copolymers, *e.g.,* entire pages 2-3, pages 8-9, paragraphs 0037-

0046 on page 3. The polymer carrier or delivery composition of PACK *et al.* also can be constructed so as to have any desired targeting agent (pages 3-4).

PACK *et al.* does not teach that the endosomal lysing agent can be operably linked to a hydrolysable or acid-labile functional group such as an ortho-ester, hydrazine or cis-acetonyl functional group.

However, at the time the invention was made, the concept of utilizing a hydrolysable or acid-labile functional group such as an ortho-ester, hydrazine or cis-acetonyl functional group so as to enhance the release of a biologically active agent from a delivery carrier is known in the prior art, as exemplified in Thorpe. More specifically, Thorpe teaches on column 19 that "the presence of such a bond would allow the generally-stable conjugate to be hydrolysed only under certain conditions, such as on exposure to an acidic pH". Thorpe further states on column 19:

> T[t]he presence of the acid-labile bond would then allow the release of the selected agent from such acid intracellular compartments. The selected agents, such as steroids, would then be free to exert their effects only when inside the target cells, and would be otherwise maintained in an active state whilst circulating the body.

A variety of acid-labile bonds could be employed to join the targeting component of a conjugate to the selected agent.

With respect to some examples of known acid-labile functional groups, Thorpe states on column 20:

Further acid-labile bonds that could be employed in accordance with the present invention incorporate ortho ester, acetal and ketal functionalities that undergo acid-catalyzed dissociation but are base-stable; and cis-aconitic.

In addition, Thorpe teaches on column 9:

Typical acid-labile linkages believed to be useful in connection with the present invention include those that employ a Schiff's base linkage, for example, linkages incorporating the condensation product of an aldehyde or ketone with a hydrazine, a hydrazide, a primary or secondary amine or their derivatives.

As such, it would have been obvious for one of ordinary skill in the art to further associate or functionally link any known acid-labile functional group such as an ortho-ester, hydrazine, or cis-acetonyl or cis-acetonitic to the endosomolytic polymer of PACK *et al.* One of ordinary skill in the art would have been motivated to do so because the concept of utilizing a hydrolysable or acid-labile functional group such as an ortho-ester, hydrazine or cis-acetonyl functional group so as to enhance the release of a biologically active agent from a delivery carrier is known in the prior art, as exemplified in Thorpe.

To the extent that the combined cited prior art does not teach poly-orthoester comprising the tertiary amine groups composed of N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide, it would have been obvious to one of ordinary skill in the art as a matter of design choice to have employed poly-orthoesters

comprising N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide as an acid-labile functional group to enhance the delivery and release of a biologically active agent from the endosome into the cytoplasm of a target cell because the monomer N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide, as evidenced by the as-filed specification, is available in the prior art, and because Thorpe teaches that any poly-orthoesters comprising tertiary amine groups would release insulin in response to a change in pH

Thus, the claimed invention as a whole was *prima facie* obvious.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 872-9106**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER